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CURRENT PROGRESS

Blood Clotting Abnormalities in Relation to Pre-Eclampsia: A Review

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AT a time when medical knowledge is increasing almost exponentially, the etiology and pathogenesis of pre-eclampsia remain enigmatic. Although significant advances in the realm of therapy have reduced the maternal mortality from this condition, the perinatal loss remains distressingly high. Even the current maternal mortality figures give little cause for complacency; Kinch[1] has reported that 1 in 15,000 mothers died from this cause.

Study and understanding have been hampered by lack of precise definition as to what constitutes "toxemia of pregnancy". Strauss,[2] in 1939, stated "The term toxemia of pregnancy has served for years and still serves as a diagnostic waste basket to cloak ignorance." Unfortunately, this statement is almost as true today. While originally it included such conditions as hyperemesis gravidarum and acute yellow atrophy of the liver,[3] the term has now come to refer to the hypertensive disorders associated with the gravid state, which are generally classified as follows:[4]

(1) Pre-eclampsia and eclampsia.
(2) Essential hypertension with or without superimposed pre-eclampsia.
(3) Chronic renal disease.

Distinction between these conditions is made on the basis of time of onset as well as on the presence or absence of pre-existing hypertension or renal disease. Pre-eclampsia has generally been thought to account for about 70% of the total,[5] although recent reports[6, 7] suggest that essential hypertension and, more particularly, chronic renal disease may account for a larger proportion than has been supposed.

The development of a safe technique for performing renal biopsy in the gravid patient[5, 7] and the electron microscopic study of renal biopsy specimens have revealed the existence of a lesion considered to be specific for pre-eclampsia. This lesion, first described by Spargo, McCartney and Winemiller[8] and later in more detail by Altchek,[7] Pollak and Nettles[5] and others,[9, 10] consists of swelling of the glomerular capillary endothelium, increase in size and number of the intercapillary cells and deposition within the cells and beneath the basement membrane of an amorphous or fibrinoid material. This lesion has been identified in pre-eclampsia and eclampsia, as well as in essential hypertension with superimposed pre-eclampsia. It has not been seen in uncomplicated essential hypertension or in chronic renal disease.[7] It is generally thought to be reversible after delivery,[6] although it has been suggested that in severe cases some of the changes may be permanent.[5]

Theories regarding the etiology and pathogenesis of pre-eclampsia are legion. Jeffcoate[11] recently reaffirmed that it is a disease of theories and summarized many of the pathophysiological factors known to be associated with it. The possible roles of the coagulation and fibrinolytic systems, however, were not included and in general have received little attention in this regard, in spite of the considerable interest they have excited in relation to the hemorrhagic complications of pregnancy. Occasional references to such a possible association appear here and there in the literature, and it is noteworthy that the most recent edition of Williams' Obstetrics includes disorders of blood coagulation in the list of possible etiological factors. It is the purpose of this review to summarize the evidence implicating disorders of coagulation and fibrinolysis in the pathogenesis of pre-eclampsia.

PATHOLOGY

It has been known for years that pre-eclampsia and eclampsia are characterized pathologically by hemorrhagic necrosis and thrombus formation in the liver, as well as by thrombosis and hemorrhage in the brain, heart and adrenals.[4, 12] Schneider,[13] in 1951, suggested that the fibrin "emboli" found at autopsy in cases of eclampsia resulted from the release of

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thromboplastic substances from the placental bed and identified the toxic material in placental extracts as thromboplastin. Page[14] had made a somewhat similar suggestion a few years earlier. Thus the concept of an association between intravascular coagulation and pre-eclampsia was introduced.

IMMUNOLOGIC EVIDENCE

Evidence of a more positive nature was provided by Vassalli, Morris and McCluskey.[15] These workers were impressed by the relationship of the coagulation process to various forms of glomerular pathology[16] and decided to study the amorphous substance found in the glomeruli of pre-eclamptic patients, employing immunological methods. Using fluorescein-tagged anti-human fibrinogen from rabbit serum, they were able to show that the material in question exhibited immunological identity with fibrinogen. They later confirmed these findings in a study which included assessment of the coagulation and fibrinolytic systems in a small number of toxemic and normal gravid patients.[17] They found no significant differences in the prothrombin time, thrombin time or levels of fibrinogen, factor V or factor VII. Nor was any difference detected in the euglobulin lysis times, lytic activity on heated or unheated fibrin plates or level of plasminogen. However, they did note a tendency to thrombocytopenia in the toxemic group, although this was not statistically significant.

DISSEMINATED INTRAVASCULAR COAGULATION

One explanation for the presence of fibrin (or a material closely related to fibrin) in the glomerulus is disseminated intravascular coagulation.[12, 16, 18] McKay and associates[19] found evidence of intravascular coagulation at autopsy in 9 out of 10 eclamptic patients. McKay[20] states that the evidence for intravascular coagulation is not as obvious in pre-eclampsia, although this may be due to the relative scarcity of tissue studies in the latter condition. McKay and Corey[21] have drawn attention to the fact that cryofibrinogen is encountered in increased amounts in patients suffering from pre-eclampsia. Smith[22] has found high levels of heparin-precipitable cold fibrinogen in the plasma of similar patients. Shainoff and Page[23] state that both these materials are similar to what they term cryoprofibrin, the presence of which they believe is associated with an increased rate of fibrin deposition within the body; they further state that it appears with slow, low-grade coagulation and that it is considered to be the most sensitive index of the action of thrombin on fibrinogen.

Animal studies have provided additional data of interest in respect of intravascular coagulation, although it should be mentioned that a satisfactory animal model of pre-eclampsia is difficult to develop. In 1963, Vassalli, Simon and Rouiller[24] perfused rabbits with varying amounts of thromboplastin at varying rates to produce intravascular coagulation. Electron microscopic examination of the glomeruli of these animals revealed an ultrastructural picture indistinguishable from that seen in pre-eclampsia. In a later study[25] they found that epsilon amino caproic acid, a competitive inhibitor of fibrinolytic activation, when administered to the animals before infusion with thromboplastin, resulted in an increased amount of fibrinogen-derived material within the glomerulus.

PLATELET ADHESIVENESS

Platelet adhesiveness is another parameter in which alterations have been noted. Wright,[26] in 1942, reported that platelet adhesiveness was increased in postoperative cases and in puerperas, but he did not report on cases with toxemia. McKay, de Bacalao and Sedlis,[27] using the method of Moolten and Vroman,[28] found that in severe pre-eclampsia platelet adhesiveness was increased by almost 40% over normal third-trimester values. Our own studies,[29] using a minor modification of the method of Salzman,[30] have shown that platelet adhesiveness is increased by about 30% in the third trimester of normal pregnancy but markedly decreased in patients in whom significant amounts of fibrinogen/fibrin proteolysis products are present. Such products may be encountered in cases of intravascular coagulation with a secondary fibrinolytic response as well as in cases of primary fibrinolysis.[31] Platelet adhesiveness values in pre-eclampsia might reasonably be expected to vary depending on whether intravascular coagulation or fibrinolysis was dominant. If active intravascular coagulation were in progress, then platelet adhesiveness might be expected to be increased.[32, 33] However, if significant fibrinolysis were taking place, the resultant fibrinogen/fibrin proteolysis products might cause platelet adhesiveness to be reduced.[29, 34] It is of interest, however, that platelet adhesiveness values have been reported to be significantly increased in women taking oral contraceptives and in a male patient receiving stilbestrol therapy for carcinoma of the prostate.[35] This observation suggests that endocrine factors must be considered in evaluating changes in platelet adhesiveness during pregnancy.

CLINICAL CORRELATIONS

Clinically it is recognized that pre-eclampsia can be complicated by bilateral renal cortical necrosis,[36] a condition which may occur in association with disseminated intravascular coagulation and which experimentally may result from it.[12, 18] Abruptio placentae also, in which there is good evidence for disseminated intravascular coagulation,[12, 29, 37] is well known for its association with pre-eclampsia (although the work of Hibbard and Hibbard[38] has recently cast doubt on the validity of this association). Although patients with pre-eclampsia rarely exhibit a severe hemorrhagic diathesis, a tendency to minor hemorrhages in the form of skin petechiae, bleeding from the gums and hematuria is not infrequently encountered.[37, 39, 40] Two recent reports[41, 42] have cited the occurrence of spontaneous rupture of the liver, and it is suggested that extensive subcapsular and intrahepatic hemorrhage may have been the initiating factor. In one of these,[41] fibrin thrombi were demonstrated within the hepatic vessels and coagulation studies revealed a prolonged thrombin time as well as thrombocytopenia, a not uncommon finding in pre-eclampsia.[37, 39, 43]

THE GENERALIZED SHWARTZMAN REACTION

Thus there is suggestive evidence indicating (1) that pre-eclampsia may be associated with abnormalities of the plasma coagulation system, possibly resulting from disseminated intravascular coagulation, and (2) that disseminated intravascular coagulation may be causative. If this is so, the factors known to predispose to intravascular coagulation must be examined. McKay[12] and others[18, 44] have suggested that intravascular coagulation may occur as a result of the generalized Shwartzman reaction (GSR). The GSR is a phenomenon produced in an experimental animal by two appropriately spaced injections of endotoxin, the result of which is the development of bilateral renal cortical necrosis and, frequently, hemorrhagic manifestations. Although the rabbit appears to be particularly susceptible to the GSR, the reaction has been produced in other animals also. Significantly, in the pregnant rabbit, only a single dose of endotoxin is required to elicit the reaction and, in a sense, pregnancy may be considered to "prepare" the animal for the GSR. Similarly, an animal may be prepared by other mechanisms, including blockade of the reticuloendothelial system, administration of corticosteroids, inhibition of the fibrinolytic system, production of generalized vasoconstriction and treatment with nitrogen mustard. With these mechanisms, as in pregnancy, the animal requires only one dose of endotoxin to produce the GSR.

Whether or not a phenomenon similar to the GSR occurs in humans and whether or not pregnancy predisposes to its occurrence are not certain, although McKay has presented provocative evidence that this is true. Certainly disseminated intravascular coagulation appears to complicate a number of obstetrical abnormalities, including abruptio placentae, amniotic fluid embolism, septic abortion, prolonged retention of a dead fetus and occasionally trophoblastic disease.

Profound physiological changes occur in the pregnant woman; those which may be of significance with regard to the GSR include well-documented increases in the plasma coagulation factors VII, VIII, IX and X, as well as fibrinogen,[37, 45, 46] although the import of such increases is not definitely known. In other words, the existence of a hypercoagulable state in pregnancy is disputed. Perhaps of greater importance is the fact that, as shown by Brakman and Astrup,[47] there is significant inhibition of urokinase-induced fibrinolysis in late normal pregnancy, while in the puerperium, fibrinolytic activity is reported to be increased.[48, 49] Also it is known that plasma levels of corticosteroids are markedly elevated during normal pregnancy,[50] although the increase is mainly in the protein-bound (and therefore presumably physiologically inactive) portion.[51] Relatively little is known about the reticuloendothelial system during pregnancy, although one recent study[52] suggests that the clearance function is unimpaired. Vasoconstriction is known to occur in pre-eclampsia, but whether this precedes or follows the glomerular deposition of fibrin has not been investigated. Of additional interest is the fact that the GSR can be prevented by heparin.[53] Heparin therapy has been used in the treatment of at least two small series of pre-eclamptic patients with successful[54] and unsuccessful[55] results.

In summary, there is evidence, both clinical and experimental, which suggests that there is an association between pre-eclampsia and abnormalities of the coagulation and fibrinolytic systems. If this is so, several questions are immediately raised:

1. Is it cause or effect?
2. Is it manifested by changes in the coagulation and fibrinolytic tests now available?
3. Would any such changes have diagnostic, prognostic or therapeutic implications?
4. In the management of such cases, is there a place for anticoagulant or fibrinolytic therapy?

Our knowledge is at present inadequate to provide answers to these questions. However, significant advances in understanding of the coagulation system and perhaps more particularly the fibrinolytic system have been made in recent years. These systems have recently been the subjects of several excellent reviews.[56-58] Application of some of the newer and more sensitive techniques for examination of these systems to accurately diagnosed cases of pre-eclampsia may provide data which will shed new and much needed light on the pathogenesis and etiology of "toxemia of pregnancy".

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